REMARKS

Claims 13-16, 18 and 39 are currently pending in this application. Claim 39 is being amended herewith. Applicant is adding herewith new Claims 40-42. Support for these amendment can be found generally throughout the specification. Applicant submits that the amendment should be entered because it places the claims in better condition for appeal. Following entry of the foregoing amendments, Claims 13-16, 18 and 39-42 will be pending. Applicants respectfully request further examination of those claims.

The Office Action

Claim 39 was rejected under 35 U.S.C. §112, first paragraph as failing to comply with the written description requirement. Applicant is amending Claim 39 herewith to overcome this rejection. The examiner has an inquiry regarding the data in Table 2. Claim 39 was rejected under 35 U.S.C. §103(a) as being obvious and unpatentable over EntreMed Overview and Attala et al. Applicants respectfully traverse the foregoing rejection. Claims 13-16 and 18 were objected to as being dependent on a rejected base claim, but would be allowable if written in independent form.

Data in the Specification

The rejection questions the data regarding the IC_{50} for 16-substituted compounds. The data shown in Table 2 is correct. The significance of the data in Table is not the level of antiproliferative activity. In fact, Table 2 shows that the level of antiproliferative activity decreases as the length of the substituted carbon chain increases at the 16-position. The object of the present invention is not to increase antiproliferative activity; the object is to reduce the rate at which 2-methoxyestradiol analogs are metabolized to a less desirable form, such as 2-methoxyestrone, which is much less active. Thus, in the context of the present invention, the precise number for the IC_{50} for the all methyl 16-substituted compound in Table 2 is essentially

irrelevant. The data in Table 2 is provided to show the trend in activity and 16-position chain length increases.

The examiner also inquires how angiogenesis can be treated. Although the level of antiproliferative activity decreases as the 16-position chain length increases, the rate at which the compound is metabolized to a much less active form is reduced. Therefore, the compound has a longer active life, which therefore makes it more effective than compounds, such as 2-methoxyestradiol, that are quickly metabolized to a much less active form, such as 2-methoxyestrone.

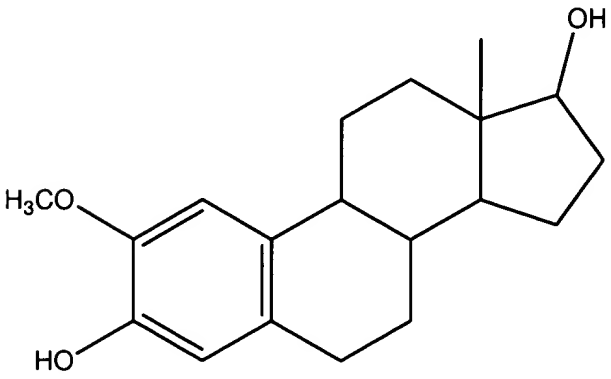
Rejection under 35 U.S.C. § 112

Claim 39 was rejected under 35 U.S.C. §112, first paragraph as failing to comply with the written description requirement. Applicant is amending Claim 39 herewith to remove the "proviso" limitation added in the previous amendment. Applicants submit that this amendment overcomes the rejection under 35 U.S.C. §112. Applicant further submits that this amendment is not a narrowing of the claim since it places the claim back in the condition it was in before the present amendment. Removal of this Section 112 issue places the claims in better condition for appeal. Therefore, entry of this amendment is appropriate. Applicants respectfully request that the amendment be entered and that the rejection under 35 U.S.C. §112 be withdrawn.

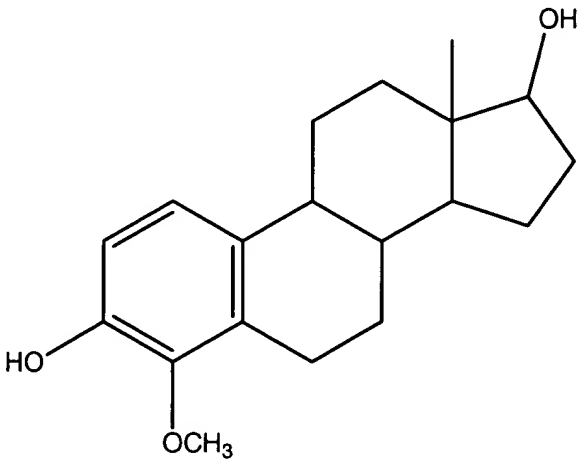
Rejection under 35 U.S.C. § 103

Claim 39 was rejected under 35 U.S.C. §103(a) as being obvious and unpatentable over EntreMed Overview and Attala et al. The rejection states that the references teach the method of inhibiting angiogenesis by 2-methoxyestradiol. The rejection further states that when the claimed compounds are substituted at the 16-position with Me and Et, they are considered homologues having similar properties to 2-methoxyestradiol and are therefore considered *prima facie* obvious. Applicants respectfully disagree.

Applicants submit that the art of estradiols is highly unpredictable. The change of a single substituent from one ring position to another ring position can change the properties of the compound from being antiangiogenic to carcinogenic. For example, 2-methoxyestradiol is antiangiogenic, while 4-methoxyestradiol is mutagenic or carcinogenic. The structures of these compounds is shown below.



2-Methoxyestradiol



4-Methoxyestradiol

The only difference between the two foregoing compounds is whether the methoxy group is at the 2-position or the 4-position of the A-ring. This difference clearly demonstrates that estradiol derivatives and analogs are highly unpredictable in their properties.

Therefore, applicants disagree that the properties of homologues of 2-methoxyestradiol are expected by those skilled in the art to be the same as that of 2-methoxyestradiol. The examiner apparently acknowledges this fact by stating, "Considering the unpredictability the claimed method of treating angiogenesis having various substituents at 16-position would not be obvious to one skilled in the art." Office Action at page 2. However, the examiner then rejects Claim 39 as being structurally similar to 2-methoxyestradiol when R_{h1} and/or R_{h2} are methyl or ethyl based solely on alleged homology. This rejection ignores the

undisputed proposition that the art of estradiols is highly unpredictable and the object of the present invention.

As stated above, the objective of the invention is not to increase the level of activity of the compound, but to reduce the rate of metabolism of the compound to a less desirable form. The invention sacrifices a small degree in the level of activity in return for a significant gain in the time that the compound will remain active; *i.e.*, not be metabolized to an undesirable form, *in vivo*. Applicants have unexpectedly discovered that if the 16-position is substituted, as presently claimed, the 16-position substituents provide steric bulk which reduces that rate at which the 17-position hydroxyl group is metabolized, thereby prolonging the active life of the compound.

The prior art relied upon by the examiner fails to appreciate the problem of metabolism of 2-methoxyestradiol to a less desirable form, such as 2-methoxyestrone. By the failure of those skilled in the art to appreciate this metabolism problem, it cannot be said that substitution of the 16-position, as claimed, would have been obvious to the skilled artisan. There is no motivation in the art to substitute the 16-position in preference to substituting the 15-position, the 14-position, the 13-position, etc. It is the selection of the 16-position for substitution, as claimed, which is unobvious.

Although the examiner has indicated the allowability of the claims if the 16-position is substituted with chain lengths greater than ethyl, applicants are amending Claim 39 to include 16-position substitution by methyl and/or ethyl. As stated above, the unobvious feature of the present invention is the selection of the 16-position for substitution which provides the advantages of the present invention. Therefore, applicants should be entitled to the claims as presently amended. Applicants request that the amendment of Claim 39 be entered because it places the claim in better condition for appeal.

New Claims

Applicant is adding herewith new dependent Claims 40 and 41. These claims specify that R_{h1} and R_{h2} are independently H and Me and R_{h1} and R_{h2} are independently H and Et, respectively. Applicant submits that new Claims 40-41 are allowable for the same reasons as Claim 39.

Allowable Claims

Claims 13-16 and 18 were objected to as being dependent on a rejected base claim, but would be allowable if written in independent form. Applicant is adding herewith new Claim 42. Claim 42 is an independent claim which includes the features of allowable Claims 13-16 and 18. Accordingly, applicants submit that new Claim 42 is in proper form for allowance in accordance with the terms of the Office Action.

Conclusion

In view of the foregoing amendments and remarks, Applicants respectfully submit that Claims 13-16, 18 and 39-42 are in condition for allowance. Such action is respectfully requested. If there are informalities remaining in the application which may be corrected by Examiner's Amendment, or there are any other issues which can be resolved by telephone interview, a telephone call to the undersigned attorney at 404-745-2408 is respectfully solicited.

Respectfully submitted,

By: Robert E. Richards
Reg. No. 29,105

KILPATRICK STOCKTON LLP
1100 Peachtree Street, NE
Suite 2800
Atlanta, GA 30309-4530
Telephone 404-815-6500
Fax 404-815-6555
Attorney Docket No. 05213-0730 (43170-219693)